Effects of Bilateral and Unilateral Stellate Stimulation on Canine Ventricular Refractory Periods at Sites of Overlapping Innervation

CHARLES W. HAWS AND MARY JO BURGESS

SUMMARY. The effects of unilateral right, unilateral left, and bilateral stellate stimulation on ventricular refractory periods at sites of overlapping cardiac sympathetic innervation were studied in 11 pentobarbital anesthetized dogs. The stellates were stimulated with 10 Hz pulses 4 msec in duration with intensities strong enough to produce T wave changes in a vertical ECG lead and just below the intensity at which control of drive of the ventricle at a 400-msec cycle length was lost. Refractory periods shortened more with left stellate stimulation, 17.8 ± 5.9 msec (mean ± SD) than with right stellate stimulation, 10.3 ± 5.1 msec, \( P < 0.001 \). During bilateral stimulation, shortening of refractory periods was no greater whether stimulation was applied first to the left and then right stimulation was added, 19.7 ± 6.9 msec, or the stimulation was applied first to the right and then left stimulation was added, 18.3 ± 6.5 msec. The shortening of refractory periods with bilateral stellate stimulation was not significantly different from that with left stellate stimulation alone. The results of this study suggest that ventricular recovery properties in areas of overlapping cardiac sympathetic innervation are less influenced by increases in tone of the right sympathetics than by increases in left sympathetic tone. In addition, the findings indicate that a bilateral increase in cardiac sympathetic tone has no greater effect on recovery properties than the effects of the left cardiac sympathetics alone.

THE VENTRICULAR distribution of the cardiac sympathetics has been defined in considerable detail in animal experiments. Although there is well defined localization of innervation by individual branches of the sympathetics to specific portions of the ventricle, there also are areas of the ventricle innervated from both the right and left sympathetic chains. The effects of imbalance of autonomic tone in portions of the cardiac sympathetics have been related to ECG waveform abnormalities and arrhythmias in patients with central nervous system disorders. Prolonged QT interval syndromes have been related to inhomogeneity of ventricular recovery properties due to autonomic imbalance. With overlapping innervation of some cardiac regions, it seemed possible that a bilateral increase in cardiac sympathetic tone might have greater effects on ventricular recovery properties in those regions than would a unilateral increase in sympathetic tone. The present study was undertaken to compare the effects of bilateral and unilateral stimulation of the cardiac sympathetics on ventricular recovery properties in areas of overlapping innervation.

Methods

Experiments were made on 11 mongrel dogs weighing 15.8 to 19.3 kg. The dogs were anesthetized with an initial intravenous dose of sodium pentobarbital, 30 mg/kg, and a continuous slow drip infusion of a solution of pentobarbital, 480 mg, in a liter of normal saline. The chest was opened with a sternal splitting incision, and ventilation was maintained with a volume pump respirator and room air. Both stellate ganglia were exposed in the thoracic cavity behind the pleura between the 1st and 2nd ribs. All connections of the ganglia except dorsal and ventral ansae were severed, and bipolar stainless steel hook electrodes were embedded in the bodies of the ganglia with the cathode proximal to the heart. The vagi were severed in the neck. The heart was suspended in a pericardial cradle and the sinus node crushed. The heart was paced at cycle lengths of 300 or 400 msec with pulses at twice diastolic threshold voltage, 2 msec in duration, delivered to a bipolar electrode placed on the right atrial appendage and to one of the unipolar electrodes placed on the ventricles. Ten to 12 unipolar hook electrodes were placed in the superficial layers of the ventricular epicardium in areas which, in previous studies, had been demonstrated to have overlapping cardiac sympathetic innervation. The other pole of these electrodes was a hook placed just beneath the skin in the chest incision. These electrodes were used to deliver both basic driving stimuli and test stimuli for refractory period measurements. Refractory periods were measured at these sites during control periods and during right, left, and bilateral stellate ganglia stimulation. To measure refractory periods unipolar, cathodal basic driving stimuli at twice diastolic threshold intensity and 2 msec in duration were delivered to one of the test sites simultaneously with the basic driving stimuli delivered to the atrium. The basic driving stimuli were applied to the test site to eliminate activation time at the test site as a factor in measuring refractory periods. The atrium was driven simultaneously to decrease the possibility of retrograde atrial activation and recipro-
cating rhythms. A second test pulse of the same intensity and duration as the basic ventricular driving stimuli was delivered to the test site after every third basic driving stimulus. This pulse initially was placed early in the cardiac cycle at a time when it did not induce a propagated response and then delayed in 1-msec increments with respect to the basic driving stimuli until a propagated response occurred. The shortest interval between a basic driving stimulus and test stimulus that induced a propagated response was taken as the refractory period.

After determining control refractory periods, first one and then the other stellate ganglion was stimulated with a train of 10 Hz, stimuli 4 msec in duration with intensities of 0.5-15 V. The strength of the stimulus was sufficient to induce T wave changes in a vertical ECG lead and below the intensity at which the dog's heart rate increased sufficiently to escape from the paced rate. These stimulus parameters are comparable to those used in previous studies from Randall's laboratory and in previous studies from our laboratory in which the distribution of the cardiac sympathetics was determined from changes in contractility or refractoriness. In studies from our laboratory, changes in refractory period duration always were found when stimulation of the sympathetics produced changes in T waveform. Monitoring the ECG was therefore a convenient method to determine that sympathetic stimulation was effective. Refractory periods were measured at the 10 to 12 test sites starting 30 seconds after initiating stimulation of one stellate ganglion. An interval of 5 minutes was allowed to elapse after nerve stimulation and measurements were repeated during a control period and during stimulation of the opposite stellate ganglion. Sites at which refractory periods shortened during both right and left stellate ganglion stimulation were considered to have overlapping cardiac sympathetic innervation. Refractory periods could be measured at these sites in 6 minutes or less, and changes induced by stimulation persisted over this period of time. In nine dogs, the effects of unilateral and bilateral stellate stimulation on refractory period durations at sites with overlapping innervation were compared in the following way. Refractory periods were measured during a control period. Left stellate stimulation then was initiated and refractory periods measured again. Right stellate stimulation then was added to the left stimulation, and measurements were repeated. The dogs were allowed to recover for 5 minutes, and observations were repeated during a control period and during unilateral and bilateral stimulation, with the stimulation this time delivered first to the right and then to both right and left stellate ganglia. Refractory period measurements obtained during each state were averaged and the standard deviations calculated. Differences in refractory periods measured during control periods and during unilateral and bilateral stellate stimulation were analyzed with the paired t-test.

## Results

T wave changes appeared in a vertical lead ECG within 5-15 seconds of initiating stellate stimulation. The changes in T waveform persisted during the period of stimulation and disappeared 1-5 minutes after stimulation was stopped. Examples of T wave changes associated with right, left, and bilateral stellate stimulation are shown in Figure 1.

In nine dogs, we identified 55 sites that received innervation from both the right and left stellate ganglia. Right stellate stimulation shortened refractory periods more than left stellate stimulation at 19 of these sites, and left stellate stimulation shortened refractory periods more than right stellate stimulation at 34 sites. There were two sites at which the change in refractory period was the same during right and left stellate stimulation. Shortening of refractory periods averaged 14.3 ± 6.2 msec during left stellate stimulation and 11.3 ± 8.6 msec during right stellate stimulation (P < 0.001).

Twenty-nine sites, including those more affected by right stimulation as well as ones more markedly affected by left stimulation, were chosen for further investigation. There were two to four such sites in each experiment. The locations of areas of overlapping innervation corresponded to previous reports and usually were found along the lateral walls of both ventricles and in the region of the pulmonary conus. Control refractory periods for all of these sites averaged 232.1 ± 15.8 msec, range 174-252 msec. There was an insignificant difference in control refractory periods of sites affected more by left stellate stimulation 232.1 ± 16.2, range 174-236 msec, and control refractory periods of sites affected more by right stellate stimulation 232.0 ± 15.1 msec, range 174-252 msec. Unilateral left stellate stimulation decreased refractory periods 17.8 ± 5.9 msec. Analyzed with the paired t-test, this was a significant decrease from control measurements, P < 0.001. Unilateral right stellate stimulation decreased refractory periods 10.3 ± 5.1 msec, a significant decrease from control values (P < 0.001). The shortening of refractory periods during unilateral left stellate stimulation was significantly more than that which occurred during unilateral right stellate stimulation, P < 0.001. During bilateral stellate stimulation, there was no significant difference in the shortening of refractory periods, whether stimulation was first applied to the left

![Figure 1](https://example.com/figure1.png)
stellate and right stellate stimulation was added, or whether the stimulation order was reversed, 19.7 ± 6.9 msec and 18.3 ± 6.5 msec, respectively. The shortening of refractory periods during bilateral stellate stimulation was not significantly greater than the changes in refractory periods that occurred with unilateral left stellate ganglion stimulation. The shortening of refractory periods during bilateral stellate stimulation was, however, significantly more than that which occurred during unilateral right stellate ganglion stimulation, \( P < 0.001 \). These findings are summarized in the graph in Figure 2.

The effects of unilateral right, unilateral left, and bilateral stellate stimulation on sites identified as having overlapping innervation in one dog are shown in Figure 3. Three sites of overlapping innervation were identified in this animal. Sites 1 and 3 were located in an area along the lateral wall of the right ventricle, and site 5 was in the region of the pulmonary conus. The bar graphs show averages of two measurements made under each condition. Although there were sites at which right stellate stimulation shortened refractory periods more than left stellate stimulation in some dogs, in the experiment illustrated, left stellate stimulation shortened refractory periods more than right stellate stimulation at all three sites. As in the averages of observation from all dogs, bilateral stellate stimulation had no greater effect on refractory periods than unilateral left stellate stimulation in this dog.

To determine if the differences in refractory periods during right and left stellate stimulation were due to differences in the intensity of stimulation of the two stellates, additional observations were made in two dogs. In one dog, right stellate stimulation intensity initially was set at 5 V, using the same criteria for stimulation intensity used in the group of experiments described above. That is, we used a stimulus intensity that produced T wave changes in a vertical lead body surface ECG, and just below the intensity at which control of drive at a 400 msec cycle length was lost. The pacing cycle then was decreased to 300 msec to permit control of drive during more intense right stellate stimulation. Refractory periods were measured at a site with overlapping innervation during control periods, with right stellate stimulation at 5 V, and during increasing intensities of stimulation up to 40 V. During right stellate stimulation with 5 V, the refractory period at the test site decreased from the control of 192 msec to 173 msec. With increased intensity of right stellate stimulation up to 40 V, there was no further decrease in the refractory period. In the other dog, control of drive at a pacing cycle of 400 msec could be maintained during right stellate stimulation with intensities up to 10 V, although stimulation intensities greater than 3 V did not produce further shortening in refractory periods. Refractory periods were measured at four sites in this dog during a control period and during right stellate stimulation with progressively increasing intensities of stimulation from 1 to 10 V, and the results are graphed in Figure 4. The measurements were made over a period of 16 minutes.

**Discussion**

The effects of unilateral stellate ganglion stimulation on ventricular refractory periods have been reported previously.\(^1\)\(^{-2}\)\(^0\) There have been no previous reports of the effects of bilateral cardiac sympathetic stimulation compared to those of unilateral stimulation on refractory periods at sites of overlapping sympathetic innervation. The findings of this study show that, in areas of overlapping innervation, left stellate stimulation shortens refractory periods more than right stellate stimulation, and the effects of bilateral stimulation are greater than the effects of unilateral right stellate stimulation. The latter relationship of the effects of unilateral right and bilateral sympathetic stimulation persists even when the intensity of right sympathetic stimulation is increased. The findings are consistent with a chemically mediated event having a cumulative effect on ventricular recovery properties until

---

**Figure 2**  Bar graph showing the means and standard deviations of the decreases in refractory periods (RP) measured at 29 sites in nine dogs during right (RSS), left (LSS), and bilateral stellate stimulation. RSS + LSS indicates stimulation first was applied to the right stellate and left stimulation was added, and LSS + RSS indicates stimulation was applied first to the left and right stimulation was added. The data were analyzed with the paired t-test, and \( P \) values are indicated.

**Figure 3**  Bar graph showing refractory periods obtained on one dog at three sites identified as having overlapping sympathetic innervation. C = control measurements, L = left stellate stimulation measurements, R = right stellate stimulation measurements, \( L + R \) = bilateral stellate stimulation with stimulation applied first to the left stellate and right stellate stimulation added, \( R + L \) = bilateral stellate stimulation with stimulation applied first to the right stellate and left stellate stimulation added.
FIGURE 4 Graph showing refractory period durations at four sites. Measurements were done during increasing intensities of right stellate stimulation, and were obtained over a period of 16 minutes. There was no greater shortening of refractory periods with 10-V stimulation intensity than with 3 V.

the limits of tissue responsiveness are reached. It is not clear why ventricular refractory periods, in areas of overlapping sympathetic stimulation, shortened more during left stellate stimulation than during right stellate stimulation, but a greater density of left innervation in these areas is a possible explanation.

Previous work by Kralios et al. showed that there is considerable overlap in the distribution of the ventromedial cardiac nerve which originates from the left sympathetic chain and recurrent cardiac nerve which originates from the right sympathetic chain. Both of these nerves innervate most of the anterior surface of the ventricles and the free wall of the left ventricle, as well as the ventricular septum. Stimulation of these two nerves also gives similar T wave changes, even though one originates from the left and the other from the right side of the sympathetic system. The ventricular sites investigated, in the study reported here, had locations consistent with innervation by the recurrent cardiac and ventromedial nerves, even though stimulation was applied to the entire stellate ganglia rather than to individual branches of the cardiac sympathetics. Very little work has been reported concerning cardiac sympathetic distribution in primates. The works of Mizeres and Randall et al., however, indicate that cardiac sympathetic nerve branches originating from the stellate and middle cervical ganglion in man and the baboon are similar to those in the dog. Although it is unlikely that the distribution of the sympathetics in humans is identical to that in dogs, it seems probable that there is overlapping innervation in other species as well as in dogs.

The relationship of autonomic imbalance to both ECG waveform and arrhythmias has received considerable attention in the literature over the last several years, especially with respect to the long QT interval syndrome. There has also been a report that indicates autonomic imbalance plays a role in arrhythmias seen in patients with subarachnoid hemorrhages, a much more common clinical entity. Autonomic imbalance associated with these disorders would be expected to produce hetrogeneity of ventricular recovery properties, which is one of the factors that Han and Moe demonstrated to be associated with enhanced vulnerability to arrhythmias in a wide variety of conditions, including left stellate stimulation.

The results of this study demonstrate a greater effect of the left than of the right stellate on ventricular refractory periods in areas of overlapping cardiac sympathetic innervation, but no greater effect of bilateral stellate stimulation on refractory periods than of left stellate stimulation alone. This response of ventricular refractory periods to bilateral sympathetic stimulation should result in a homogeneous distribution of recovery properties when there is a uniform increase in autonomic tone.

References


Downloaded from http://circ.ahajournals.org/ by guest on August 15, 2017
Effects of bilateral and unilateral stellate stimulation on canine ventricular refractory periods at sites overlapping innervation.

C W Haws and M J Burgess

doi: 10.1161/01.RES.42.2.195

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1978 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/42/2/195

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation Research_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

**Reprints:** Information about reprints can be found online at:
http://www.lww.com/reprints

**Subscriptions:** Information about subscribing to _Circulation Research_ is online at:
http://circres.ahajournals.org/subscriptions/